

REMARKS

This paper is being presented in response to the non-final official action dated March 26, 2003, wherein: (a) claims 1-17, 32-41, 44-51, and 54-57 are pending; (b) claims 38, 41, 44-51, 55, and 57 have been rejected under 35 U.S.C. § 112, ¶ 1, as lacking enablement; and, (c) claims 1-17, 32-41, 44-51, and 54-57 have been rejected under 35 U.S.C. § 103(a) as being obvious over Gehlert et al. U.S. Patent No. 5,281,624 or Foreman U.S. Patent No. 5,441,985, each in view of Dostert et al. (1997) *Euro. Neuropsychopharmacol* 7:s23-s35. Reconsideration and withdrawal of the rejections are respectfully requested in view of the foregoing amendments and following remarks.

This paper is timely filed as it is accompanied by a Petition Under 37 C.F.R. § 1.312(a) for a three-month extension of time and payment of the associated fee (\$930.00) under 37 C.F.R. § 1.17(a)(3).

I. Summary of the Amendments

A. Amendments to the Claims

Claims 38 and 55 have been canceled, without prejudice.

Claim 39 has been amended to eliminate the redundant recitation of the word "treatment" in line 1 thereof.

The preamble to claim 41 has been amended to recite a method of treating incontinence, wherein the method comprises the step of administering a therapeutically effective dose of racemic reboxetine or a pharmaceutically acceptable salt thereof to an individual.

By the foregoing amendments, two claims are being cancelled, two claims are being amended, and no claims are being newly-added. Claims 1-17, 32-37, 39-41, 44-51, 54, 56, and 57 are pending. No fee is due.

B. Amendments to the Specification

The title of the application has been amended to more closely conform to the pending claims.

The cross-reference to related applications has been amended to update the status of a previously co-pending application.

II. The 35 U.S.C. § 112, ¶ 1, Rejection is Moot

Claims 38, 41, 44-51, 55, and 57 have been rejected under 35 U.S.C. § 112, ¶ 1, because, according to the action, the specification "while being enabling for treating

incontinence, does not reasonably provide enablement for preventing incontinence.” See p. 2 of the action.

Claims 38 and 55, which previously recited a method of preventing incontinence, have been canceled, without prejudice. Additionally, claim 41 has been amended to omit recitation of the method of “preventing” incontinence. Claims 44-51 and 57 depend from claim 41. In view of the foregoing claim amendments, it is respectfully submitted that the pending claims are sufficiently enabled. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. The 35 U.S.C. § 103(a) Rejection is Traversed

All of the pending claims have been rejected under 35 U.S.C. § 103(a) as being obvious over Gehlert et al. U.S. Patent No. 5,281,624 or Foreman U.S. Patent No. 5,441,985, each in view of Dostert *et al.* (1997) *Euro. Neuropsychopharmacol* 7:s23-s35, (hereafter the “1997 Dostert article”). See pp. 3 and 4 of the action. A response to the obviousness rejection is set forth below.

A. Proper Basis for a § 103(a) Rejection

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings of a plurality of references. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, and not based on the applicants’ own disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); *see also* MPEP § 2143 (8th ed. (Rev. 1) Feb. 2003).

The examiner bears the burden of establishing a *prima facie* case of obviousness and “can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.” *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). To support a conclusion that a claimed combination is obvious, either (a) the references must expressly or impliedly suggest the claimed combination to one of ordinary skill in the art, or (b) the examiner must present a convincing line of reasoning as to why a person of ordinary skill in the art would have found the claimed invention to have been obvious in light of the teachings of the references. *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

B. No *Prima Facie* Case of Obviousness Has Been Made or Exists and, therefore, the § 103(a) Rejections are Traversed

Neither of the combinations of (1) the Foreman patent and the 1997 Dostert article or (2) the Gehlert patent and the 1997 Dostert article provides the requisite suggestion or motivation to modify or combine their respective teachings to arrive at the claimed invention. Furthermore, even if such suggestion or motivation did exist, which it does not, there is no reasonable expectation that either of the combinations would yield success. Thus, no *prima facie* case of obviousness has been made or exists based on the combination of the applied publications. Accordingly, reconsideration and withdrawal of the § 103(a) rejection are respectfully requested.

1. The Combination of the Foreman Patent in View of the 1997 Dostert Article Does Not Render the Claimed Invention Obvious

According to the action, the claimed invention is obvious over the disclosures of the Foreman patent in view of the 1997 Dostert article. The rejection is traversed, and reconsideration and withdrawal of the rejection are respectfully requested.

At page S23, the 1997 Dostert article states that “reboxetine has been shown to be a selective noradrenaline reuptake inhibitor (NARI),” and suggests that it possesses potent and selective NARI properties. Such a suggestion of selectivity, however, should be limited to a selectivity for the NARI receptors over the α -adrenergic, β -adrenergic, and muscarinic cholinergic receptors, as described at page S24. The article proceeds to state that “[t]he (S,S)— enantiomer is more potent than its enantiomeric counterpart in inhibiting ... noradrenaline reuptake” in mice. See p. S24 of the 1997 Dostert article.

The Foreman patent discloses a method of treating urinary incontinence by employing certain bicyclic compounds (preferably tomoxetine or tomoxetine hydrochloride), which inhibit norepinephrine reuptake and which have a negligible anticholinergic effect. See col. 6, lines 61-61, and col. 8, lines 56-59. Importantly, the Foreman patent also describes in great detail the art concerning urinary incontinence treatment methods. See col. 2, line 54 to col. 6, line 57. Nocturnal enuresis is one type of urinary incontinence discussed in the Foreman patent. See col. 1, lines 26-39. The Foreman patent acknowledges that “tricyclic antidepressants have been the most effective pharmacologic agents for treating nocturnal enuresis,” and that nortriptyline, amitriptyline, desipramine are effective tricyclics, while imipramine is the most widely-used of the tricyclics. See col. 2, lines 60-64. According to the Foreman patent, “[t]here have been at least five different proposed mechanisms that have been suggested as the basis for [imipramine’s] effect for treating incontinence.” See col. 3, lines 64-66. For example, imipramine has been demonstrated to have anticholinergic activity, antispasmodic activity, local anesthetic activity, and been shown to inhibit the reuptake of both norepinephrine and serotonin (5-HT). See col. 3 line 67 to col. 6, line 2. Additionally, the

Foreman patent acknowledges, in addition to the then art-recognized role of norepinephrine in lower urinary tract physiology, that serotonergic neurons and receptors have also been shown to have effects on lower urinary tract functions. See col. 6, lines 3-6.

In view of the reviewed art, the Foreman patent acknowledges that:

... it is apparent that while imipramine and other tricyclic antidepressants are used to treat a variety of lower urinary tract disorders, **the predominant mechanism responsible for these clinical effects remains unclear**. Clearly these compounds have multiple mechanisms. However, which mechanism primarily responsible for any of the mentioned utilities is subject to continuing experimentation and discussion.

See col. 6, line 14-20 (emphasis added). In conclusion, the Foreman patent states:

Thus, the literature is, at best, uncertain as to the biological mechanism underlying the ability for the tricyclic antidepressants to treat incontinence. Moreover, it is clear that to the extent that any one or combination of these mechanisms may be useful for producing the end result, the compounds also have mechanisms which result in undesirable side effects. As noted above, imipramine and the other tricyclic antidepressants do possess a strong anticholinergic effect which likely results in the aforementioned side effects. Not only are such side effects annoying, but they may limit the effectiveness or even the use of such drugs. Accordingly, the need to discover drugs useful for treating incontinence without such side effects is evident.

See col. 6, lines 44-57 (emphasis added).

On the basis of the complete teachings of the Foreman patent and the 1997 Dostert article, a person of ordinary skill in the art as of the present application's filing and priority dates would not have been motivated to substitute the (S,S) reboxetine disclosed in the 1997 Dostert article in place of the bicyclic compounds disclosed in the Foreman patent. Based on the Foreman patent's teachings that compounds possessing serotonergic activity are thought to have a desirable effect on the lower urinary tract function, one skilled in the art would not have been motivated to substitute a potent norepinephrine reuptake inhibitor, without knowing whether that agent also deleteriously affected the serotonergic receptors. Based on the uncertainty in the art as to the biological mechanism underlying the ability for tricyclics to treat incontinence, a person of ordinary skill in the art is no more motivated to substitute reboxetine instead of another tricyclic. Thus, claim 1 and claims dependent therefrom are not obvious.

Additionally, based on the Foreman patent's statements concerning the uncertainty as to the biological mechanism by which tricyclics appear to treat incontinence, and the Foreman patent's disclosure of using bicyclics to treat incontinence, one skilled in the art would not have been motivated to use a tricyclic, notwithstanding the disclosure in the 1997 Dostert article. Thus, claims 39 and 41 and claims dependent therefrom are not obvious.

Prior to the disclosure in the present application, it was not publicly known that (S,S) reboxetine exhibited a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i)

of at least about 5000. Given certain statements in the Foreman patent that compounds responsible for inhibiting serotonin reuptake also advantageously affect the lower urinary tract functions (see col. 6, lines 3-6), a person of ordinary skill in the art would not necessarily use a compound as claimed to treat urinary incontinence. Moreover, because the pharmacological selectivity limitation of claim 1 is not found in the Foreman patent and that compounds possessing such selectivity are not disclosed in the prior art to treat urinary incontinence, no *prima facie* case of obviousness exists.

In view of the foregoing, reconsideration and withdrawal of the rejection are respectfully requested.

2. The Combination of the Gehlert Patent in View of the 1997 Dostert Article Does Not Render the Claimed Invention Obvious

According to the action, the claimed invention is obvious over the disclosures of the Gehlert patent in view of the 1997 Dostert article. The rejection is traversed, and reconsideration and withdrawal of the rejection are respectfully requested.

The Gehlert patent identifies norepinephrine as “one type of neuron,” and that the bicyclic compounds of the Gehlert patent’s invention “indirectly stimulate neurons by inhibiting norepinephrine reuptake.” See col. 1, lines 11-19. According to the Gehlert patent, this inhibition occurs “in an unexpectedly selective and potent manner.” See col. 6, lines 30-32. Furthermore, the Gehlert patent states that the bicyclic compounds are “selective and potent inhibitors of norepinephrine uptake” and further that such compounds “are useful to treat urinary incontinence” because of “the known interaction of the norepinephrine with the urinary system.” See col. 1, lines 34-36 and lines 65-67. The bicyclic compounds disclosed in the Gehlert patent are structurally very similar to the bicyclic tomoxetine specified in the Foreman patent.

As discussed above (in section III.B.1 of this paper), the 1997 Dostert article states that “reboxetine has been shown to be a selective noradrenaline reuptake inhibitor (NARI),” and suggests that it possesses potent and selective NARI properties, specifically a selectivity for the NARI receptors over the α -adrenergic, β -adrenergic, and muscarinic cholinergic receptors. The article proceeds to state that “[t]he (S,S)— enantiomer is more potent than its enantiomeric counterpart in inhibiting ... noradrenaline reuptake” in mice. See p. S24 of the 1997 Dostert article.

The Gehlert patent and the 1997 Dostert article, when considered together in isolation, might suggest that any material showing a selectivity for norepinephrine reuptake over the α -adrenergic, β -adrenergic, and muscarinic cholinergic receptors can be used to treat urinary incontinence. The mere fact, however, that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests

the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01 (8th Ed. (Rev. 1) Feb. 2003). Notably, the Gehlert patent's disclosure does not describe/define the basis for the selectivity of its bicyclic compounds (i.e., over what receptors do the bicyclic compounds show a preferential selectivity for the norepinephrine receptors?). Certainly, the Gehlert patent does not suggest that the selectivity that the bicyclic compounds show for norepinephrine reuptake receptors is preferred over that of the α -adrenergic, β -adrenergic, and muscarinic cholinergic receptors. There are many other neurons which also could account for the mechanism affecting urinary incontinence. Thus, the Gehlert patent's disclosure and that of the 1997 Dostert article do not provide adequate motivation/suggestion to the skilled artisan to substitute a tricyclic compound (e.g., reboxetine) in place of the bicyclic compound and expect that the tricyclic compound will behave in the same manner and with the same desirable (though unclear) selectivity suggested by the Gehlert patent's disclosure. Consequently, no *prima facie* case of obviousness exists based on the combination of the Gehlert patent and the 1997 Dostert article.

Moreover, given that an obviousness determination must include a determination of the scope and content of all of the prior art, there are other prior art publications which, when also considered, cast sufficient doubt on a suggestion that any material showing a selectivity for norepinephrine reuptake over the α -adrenergic, β -adrenergic, and muscarinic cholinergic receptors can be used to treat urinary incontinence. See *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). (stating that the references must be considered as a whole and must suggest the desirability and, thus, the obviousness of making the combination); MPEP § 2141 (8th ed., rev. 1 Feb. 2003). As discussed above (in Section III.B.1. of this paper), the Foreman patent casts sufficient doubt on the mechanism by which urinary incontinence can be treated even with tricyclics. Specifically, the Foreman patent states that "[t]he literature is, at best, uncertain as to the biological mechanism underlying the ability for the tricyclic antidepressants to treat incontinence." See col. 6, lines 44-46 of the Foreman patent.

The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the import of each reference's disclosure should be weighed to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *In re Young*, 18 USPQ2d 1089 (Fed. Cir. 1991); MPEP § 2143.01 (8th Ed. (Rev. 1) Feb. 2003). The Foreman patent was filed within months of the Gehlert patent and shares the same assignee — Eli Lilly and Company, Indianapolis, Indiana. The Foreman patent is at least some evidence that scientists within the same organization did not have a consistent understanding of the biological mechanism by which urinary incontinence could be treated. To wit, the Foreman patent asserts that even

those practicing in the art outside of the organization (as represented by the literature reviewed in the patent) were uncertain as to the mechanism. In view of such uncertainty, a person of ordinary skill in the art would not have been motivated to substitute a material showing a selectivity for norepinephrine reuptake over the α -adrenergic, β -adrenergic, and muscarinic cholinergic receptors (as disclosed in the 1997 Dostert article) in the place of a particular class of bicyclics having some undefined selectivity for norepinephrine reuptake (as disclosed in the Gehlert patent) to treat urinary incontinence. It is respectfully submitted that the totality of the prior art must be considered, and proceeding contrary to accepted wisdom/teachings in the art is evidence of non-obviousness. See *In re Hedges*, 228 USPQ 685 (Fed. Cir. 1986); see also MPEP § 2145(X)(D)(3) (8th ed., rev. 1 Feb. 2003).

Because the requisite suggestion and motivation are lacking, no *prima facie* case of obviousness exists based on the prior art and, therefore, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing, entry of amendments to the specification, cancellation of claims 38 and 55, entry of the amendments to claims 39 and 41, reconsideration and withdrawal of the rejections, and allowance of all pending claims (i.e., claims 1-17, 32-37, 39-41, 44-51, 54, 56, and 57) are respectfully requested.


Should the examiner wish to discuss the foregoing, or any matter of form or procedure in an effort to advance this application to allowance, he is urged to contact the undersigned attorney.

Respectfully submitted,

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